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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/684,554	10/06/2000	John F. Engelhardt	875.024US1	4157

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,554	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8-11,19-21,23-37,41-43,46-54,58 and 59* is/are pending in the application.

4a) Of the above claim(s) *2, 3, 8, 10, 11, 21, 23-37, 41-43, 48-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,19,20,46,47,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed October 22, 2004 in response to the Office Action of April 19, 2004 and the Interview of September 7, 2004 is acknowledged and has been entered. Claims 4, 55-57 have been cancelled. Claims 1, 9, 19, 20, 46, 47, 58 and 59 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Addressing applicants arguments that claim 10 should be examined in the instant application. Claim 10 as written is drawn to an invention that does not include promoters because the claim makes reference that the cis-acting element is "not a heterologous promoter." Therefore, claim 10 reads on enhancers that belong to a group that has not been elected. Applicants' argument is that the cis-acting element can include either enhancers or promoters, this argument has already been addressed in the Office Action pf March 11, 2003 and the original Election/Restriction requirements of August 26, 2002, and both repsonses have indicated that claim 1 is a linking claim. Only upon allowance of claim 1 will the groups including the enhancers be rejoined, this is provided claim 1 has not been amended to the point of excluding enhancers.

Claim Rejections - 35 USC § 112

The rejection of claims 58 and 59 (note claim 57 has been deleted in the instant amendment) under 35 U.S.C. 112, first paragraph, as failing to comply with the written

description requirement **is maintained**. Applicants have pointed to page 91, lines 9-18 and page 10, lines 9-20 as providing written description for the claim limitation that "do not contain a heterologous splice site" or "are not splicing vector." The specific section applicants points to in the specification does not have support this amendment. At best the cited specification section are silent regarding the presence or absence of the splice site. A contemplated embodiment includes the entire CFTR transgene on one vector but does not specifically mention that there is no transcription splice site in the vector.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 9, 46, 47, 55, 56 under 35 U.S.C. §102(e) as being anticipated by Engelhardt et al. (U.S. Pat. No. 6,436,392 B1) **is maintained** for reasons of record.

Applicant's amendments and arguments directed to the newly amended claims have been fully considered but fail to persuade. Applicants' arguments are that the newly amended claims require that the cis-acting heterologous transcriptional regulatory element (directly) regulates transcriptional expression of the gene product encoded by the open reading frame in a host cell contacted with the first and second rAAVs. In response to applicant's argument that the references fail to show certain features of applicant's invention that the reference does not regulate transcriptional expression of the gene product encoded by the other rAAV vector. Applicants underlying arguments is that the gene product must be solely contained in the second vector, however, this limitation is not recited in the rejected claims. An open reading frame (ORF) is a DNA sequence that potentially encodes a protein. ORFs often have all the intervening sequences (introns) removed, but this is not a requirement because there can be many

proteins that are differentially spliced. ORFs are usually detected because the DNA stretches do not contain stop codons. The absence of stop codons implies that the DNA is a gene that codes for a protein. The limitation that the ORF encodes a therapeutic product does not exclude splice donor or splice acceptor sites from the DNA construct comprising an open reading frame. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The instant invention is drawn to a composition comprising two recombinant adenovirus vectors. The composition requires two recombinant AAV constructs that comprise a 5'and 3' ITR with a heterologous DNA sequence in between (claim 1). The vectors comprise a promoter (a heterologous transcriptional element) linked to the open reading frame (claims 9, 11, 46 and 47). Engelhardt et al. disclose a host cells comprising at least two recombinant AAV vectors each comprises a 5' and 3' LTR, a heterologous DNA segment (open reading frame). The second DNA comprising a portion of an ORF operably linked to a promoter (see claim 9 and figure 14A, figure 19B column 3, lines 20-42). The promoter on vector 1 is responsible for the transcriptional regulation of the portion of the ORF gene product on the second vector. Without the concatamer formation the gene product on the second vector would not be transcribed in a host cell. The promoter on vector 1 is responsible for the transcription of the gene product on vector 2. Therefore, the instant invention remains anticipated by Engelhardt et al.

The rejection of claims 1, 9, 46, 47 under 35 U.S.C. 102(e) as being anticipated by Couto et al. (U.S. Pat. No. 6,200,560) or Couto et al. (U.S. Pat. No. 6, 221,349) **is withdrawn** in view of applicants' amendments.

The rejection claims 1, 9, 19, 20, 46, 47 and newly added claims 55, 56 and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by Rendahl et al. (Nature Biotechnology 1998) **is maintained** for reasons of record.

Applicant's amendments and arguments directed to the newly amended claims have been fully considered but fail to persuade. Applicants' arguments are that the newly amended claims require that the cis-acting heterologous transcriptional regulatory element (directly) regulate transcriptional expression of the gene product encoded by the ORF in a host cell contacted with the first and second rAAVs. However, the claims as written are not this narrow. The system disclosed by Rehndahl et al. comprises a CMV promoter (cis-acting regulatory element) which effects transcription of the tTA (which is located cis of the CMV promoter) and through the expression of tTA does the cis-acting regulatory element effect the transcription of the gene located on the second rAAV. Rehndahl et al. discloses the *in vi*vo regulation of gene expression following co-injection of two separate recombinant adeno-associated virus vectors, one encoding an inducible murine erythropoietin transgene (a therapeutic gene) and the other a transcriptional activator, directly into the skeletal muscle of adult immunocompetent mice. Construct one (rAAV-CMV-tTA) comprises the tetracylince responsive transactivator and the mouse protamine polyadenylation site. Vector two (rAAV-(tetO)7-minCMV-mEPO) tetracycline responsive element reiterated 7 times regulating the minimal CMV promoter bovine growth hormone

polyadenylation site. In this instance the expression tTA from one AAV construct regulates the expression of the inducible murine erythropoietin transgene which is found on the other AAV construct. The CMV promoter is functional in a host cell. The vectors are shown to be expressed in the same cells indicating that these cells comprise both AAV constructs. Therefore, the instant invention remains anticipated by Rendahl et al.

Double Patenting

The rejection of claims 1, 9, 46 and 47 and newly added claims 55 and 56 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-15 of U.S. Patent No. 6,436,292 **is maintained** for reasons of record. The host cells of the patented methods comprises at least two recombinant AAV vectors each comprises a 5' and 3' LTR, a heterologous DNA segment (open reading frame). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant invention does not exclude the compositions used in the patented methods.

Applicant's amendments and arguments directed to the newly amended claims have been fully considered but fail to persuade. Applicants' arguments are that the newly amended claims require that the cis-acting heterologous transcriptional regulatory element (directly) regulates transcriptional expression of the gene product encoded by the open reading frame in a host cell contacted with the first and second rAAVs. In response to applicant's argument that the references fail to show certain features of applicant's invention that the reference does not regulate transcriptional expression of the gene product encoded by the other rAAV vector. Applicants underlying arguments is that the gene product must be solely contained in the second

vector, however, this limitation is not recited in the rejected claims. An open reading frame (ORF) is a DNA sequence that potentially encodes a protein. ORFs often have all the intervening sequences (introns) removed, but this is not a requirement because there can be many proteins that are differentially spliced. ORFs are usually detected because the DNA stretches do not contain stop codons. The absence of stop codons implies that the DNA is a gene that codes for a protein. The limitation that the ORF encodes a therapeutic product does not exclude splice donor or splice acceptor sites from the DNA construct comprising an open reading frame. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The instant invention is drawn to a composition comprising two recombinant adenovirus vectors. The composition requires two recombinant AAV constructs that comprise a 5'and 3' ITR with a heterologous DNA sequence in between (claim 1). The vectors comprise a promoter (a heterologous transcriptional element) linked to the open reading frame (claims 9, 11, 46 and 47). Engelhardt et al. disclose a host cells comprising at least two recombinant AAV vectors each comprises a 5' and 3' LTR, a heterologous DNA segment (open reading frame). The second DNA comprising a portion of an ORF operably linked to a promoter (see claim 9 and figure 14A, figure 19B column 3, lines 20-42). The promoter on vector 1 is responsible for the transcriptional regulation of the portion of the ORF gene product on the second vector. Without the concatamer formation the gene product on the second vector would not be transcribed in a host cell. The promoter on vector 1 is responsible for the transcription of the gene product on vector 2. Therefore, the instant invention remains anticipated by Engelhardt et al.

Conclusion

No claims allowed.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER
2/22/05